molecular dynamics simulations we investigate inter- and intra-molecular interactions driving the self-assembly and formation of the morphology of supramolecular DAs. More specifically, we investigate the self-assembly of camptothecin-based DAs, which have been shown to form cylindrical supramolecular assemblies with a well-defined structure. For each DA, we examine the self-assembly process from random using long-time all-atomistic molecular dynamics simulations (> 200 ns). We also examine the structure of pre-assembled cylindrical supramolecular assembly, comparing the cylindrical radii with reported experimental measurements. We also characterize the distribution of hydrogen bonds, Cl- ions, as well as the secondary structure formation in the peptide over time. Our findings can help add further insight into the rational design of supramolecular assemblies.

1.Cheetham, A. G.; Zhang, P. C.; Lin, Y. A.; Lock, L. L.; Cui, H. G., Supramolecular Nanostructures Formed by Anticancer Drug Assembly. Journal of the American Chemical Society 2013, 135 (8), 2907-2910.
2.Cui, H. G.; Pashuck, E. T.; Velichko, Y. S.; Weigand, S. J.; Cheetham, A. G.; Newcomb, C. J.; Stupp, S. I., Spontaneous and X-ray-Triggered Crystallization at Long Range in Self-Assembling Filament Networks. Science 2010, 327 (5965), 555-559.

1587-Pos Board B538

Simulating the Serpin Latency Transition at Atomic Resolution

Patrick Wintrode[1], Pietro Faccioli[2], Silvio a Beccara[3], Anne Gershenson[4], Giorgia Cazzolli[5], Fang Wang[1].
[1]Pharmaceutical Sciences, University of Maryland, Baltimore, MD, USA, [2]Physics, University of Trento, Trento, Italy, [3]Interdisciplinary Laboratory for Computational Science, Fondazione Bruno Kessler, Trento, Italy, [4]Biochemistry and Molecular Biology, University of Massachusetts, Amherst, MA, USA, [5]Physics, University of trento, Trento, Italy.

Protease inhibition by serpins requires a massive conformational transition from an active, metastable state to an inactive, stable state. Similar reactions can also occur in the absence of proteases, and these latency transitions take hours, making their time scales many orders of magnitude larger than are currently accessible using conventional molecular dynamics simulations. Using a path integral based variational framework termed the Dominant Reaction pathways (DRP) method, we have successfully simulated the latency transition for several serpins in all atom detail using a physics based force field. The DRP method can clearly distinguish serpins which spontaneously perform the latency transition from those that do not. Additionally, the DRP simulations successfully reproduce the effects of mutations on the rate of the latency transition. For the serpin plasminogen activator inhibitor 1 (PAI-1) we find a long lived intermediate state along the active to latent pathway. This state shares several features that characterize a so called pre-latent state that has been detected experimentally, including partial insertion of the reactive center loop into beta-sheet A and removal of strand one from sheet C, and we propose that our intermediate represents the pre-latent state. Analysis of the energetics of the transition identifies a small subset of residues that provide the bulk of the energy change during the transition, and these residues include many known sites of disease associated mutations. Docking a known PAI-1 inhibitor to our pre-latent state identifies a pocket that it shares with the latent structure and which may provide a target site for computational drug screening. Comparison of the latency transitions in different serpins reveals how sequence variation has modulated conformational plasticity in this family of unusually labile proteins. The DRP method should prove applicable to conformational changes in other large proteins.

1588-Pos Board B539

Estimating the Diffusion Constant from Noisy Trajectories

Peter K. Relich, Keith A. Lidke, Mark J. Olah.
Physics, UNM, Albuquerque, NM, USA.

The motion of a single particle dominated by Brownian motion can be described by a single parameter D, the diffusion coefficient. The estimation of D from a discrete sequence of noisy observations is a fundamental problem in single-molecule experiments. Originally, D was estimated from a linear regression of the mean squared displacement (MSD). The MSD regression is plagued with issues involving, but not limited to, determining the optimal number of data points to regress from and the regression does not utilize all of the localization information provided from typical trajectory information. The drawbacks of the MSD analysis furthered investigations into different estimators, such as the maximum likelihood. However, prior solutions to the maximum likelihood estimation problem do not utilize the information from individual localization precisions which results in inaccurate likelihood distributions for short particle trajectories under realistic measurement errors. We present direct solutions to this problem using three different derivation techniques, including Markov's method for estimating random flights. We also provide an implementation in C++ that outperforms prior maximum likelihood estimators in accuracy without compromising speed.
We then map the likelihood of D from our estimator to an approximate analytical posterior distribution using classic Bayesian analysis techniques. Our analytical distribution can be parameterized by three coefficients which allows for a robust calculation on the quality of a D estimate given an arbitrary set of data.

1589-Pos Board B540

Molecular Insights into the Signaling Mechanism of the Histidine Kinase CheA within an Intact Bacterial Chemosensory Array

C. Keith Cassidy[1], Benjamin Himes[2], Frances Joan D. Alvarez[2], Juan R. Perilla[1], Jun Ma[2], Gongpu Zhao[2], Peijun Zhang[2], Klaus Schulten[1].
[1]Physics, University of Illinois, Champaign, IL, USA, [2]Structural Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

The chemotactic response in bacteria relies on the formation of large, highly ordered complexes of sensory proteins, known as chemosensory arrays, which mediate the transduction and regulation of signals that ultimately control cellular motility. Although, a coarse representation of the array's extended organization has recently been sketched out, an outstanding problem concerns the detailed description of the molecular events occurring within the array during signaling. Progress in this area necessitates a high-resolution understanding of the intact chemosensory array structure. Utilizing cryo-electron tomography and 3D subvolume averaging, we have derived density maps of a resolution sufficient for the construction and refinement of an atomic model of the chemosensory array's core structure. Large-scale, all-atom molecular dynamics (MD) simulations of an atomic model of the array unit cell, 1.2 million atoms in size, have revealed the molecular details of the interaction interfaces between the receptor, CheA, and CheW proteins, as well as a distinctive conformational change in CheA kinase domain. Mutagenesis and chemical cross-linking studies have further confirmed the important roles of specific residues at these critical interaction interfaces.

1590-Pos Board B541

Calculation of Cholesterol Binding Affinity for Pentameric Ligand-Gated Ion Channels

Reza Salari[1], Jerome Henin[2], Grace Brannigan[1].
[1]Physics and Center for Computational and Integrative Biology, Rutgers University - Camden, Camden, NJ, USA, [2]Laboratoire de Biochimie Théorique, CNRS, Paris, France.

Cholesterol has been shown to play a critical role in the function of ion channels and many types of ion channels partition into cholesterol-rich membranes. Several Eukaryotic pentameric ligand-gated ion channels, including the nicotinic Acetylcholine Receptor and the GABA(A) receptor, are highly sensitive to the cholesterol content of reconstitution mixtures or native membranes, but the binding interactions between cholesterol and these receptors are largely uncharacterized. Since the mechanisms for modulation by cholesterol are likely to be at least partially through direct interactions via specific binding, cholesterol molecules may form an essential component of the native structure for some of these receptors. We recently proposed, based on the crystal structure of the glutamate-gated chloride channel (GluCl) from C. elegans solved in complex with the lipophilic ligand ivermectin, that cholesterol molecules could bind to these intersubunit sites in a pose analogous to that of ivermectin in the absence of other modulators, and tested this model in the homologous GABA(A) receptor using Molecular Dynamics (MD) simulations. Here we employ computational free energy calculation methods to provide a quantitative estimate of the binding affinity of cholesterol for these sites on GluCl and other pentameric ligand-gated ion channels, demonstrating that these sites are likely to be partially occupied at physiological concentrations of cholesterol.

1591-Pos Board B542

Characterization of Transiently Stable Structural Motifs in Intrinsically Disordered Proteins using Free Energy Simulations

Rainer Bomblies, Manuel Luitz, Martin Zacharias.
Physik-Department, Technical University Munich, Garching, Germany.

A significant fraction of protein-protein interactions especially in eukaryotic cells involves intrinsically disordered proteins (IDP). Even intrinsically disordered proteins may contain transiently stable structural motifs such as alpha-helical conformations or other secondary structure motifs. The stability of these motifs can play an important role for the interaction with other proteins of the cell. Due to the limited sampling standard molecular dynamics (MD) simulations may not be useful to characterize the relative population and free energy of conformational states of IDPs. We have developed a new approach to estimate the free energy change for small segments along a disordered protein to adopt a given secondary structure (e.g. an alpha-helical conformation) relative to an unfolded state. The approach is based on umbrella sampling (US)